REMARKS

Claims 33-39 are currently pending in the present application.

Claims 22-32 and 40-41 have been canceled, without prejudice to the filing of one or more divisional applications directed to the subject matter thereof. Claims 33-35 have been amended to incorporate the subject matter of the canceled claims from which they previously depended. It is respectfully submitted that the amendments made herein are supported by the Specification and the original claims. Accordingly, the amendments made herein introduce no new subject matter. The amendments made herein do not narrow the pending claims in any way. Additionally, no additional claims fees are necessitated. A complete listing of all claims ever presented in accordance with 37 C.F.R. §1.121(c)(1) is set forth herein. Thus, entry of the amendments made herein is proper and respectfully requested.

In the Office Action, the Examiner objects to claims 33-37 as not having formula (I) and formula (II) set forth therein. As stated above, Applicant has amended the claims to incorporate the subject matter of the dependent claims from which they previously depended including the cited formulae. Accordingly, removal of the objection is respectfully requested.

In the Office Action, the Examiner rejects claim 37 under 35 U.S.C. §112, first paragraph, as lacking enablement and failing to comply with the written description requirement. Specifically, the Examiner contends that the inhibition of tumor activity is not described in the Specification in such a way as to convey to one of ordinary skill in the art that the inventors had possession of the claimed invention at the time the application was filed. Additionally, the Examiner contends that while the Specification is enabling for methods of using the disclosed compositions for the treatment of colon tumors and ovarian tumors, it does not reasonably enable the use of the disclosed compositions for the treatment of other tumors.

Applicant respectfully traverses the Examiner's rejection and the arguments and contentions set forth in the Office Action in support thereof, for the following reasons. Applicant submits that one of ordinary skill in the art, upon reading Applicant's Specification, would be capable of and enabled to design and carry out any necessary protocol or clinical

design experiment as may be necessary and expected for determining an appropriate dosage, regimen and/or route of administration for any of the disclosed types of tumors. Applicant submits herewith a Declaration under 37 C.F.R. §1.132 of Nikolai Graf v. Keyserlingk, Ph.D. (hereinafter referred to as "the Declaration") as additional support that the Specification is enabling and that the invention is adequately described with respect to the full scope and breadth of pending claim 37.

More specifically, as detailed in the Declaration, one of ordinary skill in the art, upon reading the Specification, would understand and be equipped with the knowledge necessary to design a protocol, such as described in the Declaration. (*See*, the Declaration, paragraph 6). The dosages and frequency thereof for any of the various routes of administration described can be evaluated either in a human clinical trial or in an *in vitro* study to determine an appropriate and efficacious method of treatment for any given type of tumor. As set forth in the Declaration, the techniques and parameters of clinical protocol design are part of the normal practice and knowledge for a clinician/physician active in oncology.

As set forth in the Declaration, the use of pre-clinical animal studies for the determination of an initial dosage in a human clinical trial is well known in this field, *i.e.*, the research of anti-tumor agents. Moreover, the *in vitro* analysis of suitable starting dosage levels and/or the activity of specific compounds with respect to specific carcinoma cell lines can be readily evaluated as described in the Declaration. (*See*, the Declaration, paragraphs 12-14).

Accordingly, it is respectfully submitted that one of ordinary skill in the art would possess the requisite knowledge and information upon review of the disclosure set forth in Applicant's Specification, to enable such a person to design and carry out the ordinary and expected (and not undue) experimentation that would be required to determine a suitable dosage, regimen and route of administration for the treatment of a specific type of tumor. Moreover, it would be recognized by those skilled in the art that such experimentation would be required, given the potential variety of patient types, ages and sensitivities, as well as the various states of progression of disease that may be encountered in a given patient pool. (*See, e.g.*, Applicant's Specification, p. 7, lines 13-21).

Moreover, Applicant respectfully submits that information showing that Applicant had possession of the invention is set forth in the Specification to a sufficient extent that one of ordinary skill in the art would recognize that Applicant had possession of claimed invention. More specifically, for example, at paragraphs [0048] – [0051], the suitable range of dosages is described. For example, at paragraph [0045], various suitable routes of administration are described and, for example, in paragraphs [0053] – [0062], the various types of formulations into which compositions disclosed in Applicant's specification can be incorporated for the treatment of various tumors are described. Accordingly, Applicant submits that upon reading the Specification, one of ordinary skill in the art would recognize that Applicant was in possession of the claimed invention.

Thus, as described above and in view of the Declaration and attachments thereto, Applicant respectfully submits that the Specification is fully enabling of claim 37 and that the invention as claimed, is supported by the Specification. Reconsideration and withdrawal of the rejections under 35 U.S.C. §112, first paragraph, are respectfully requested.

In the Office Action, the Examiner rejects claims 33-37 under 35 U.S.C. §112, second paragraph, as being indefinite. Specifically, the Examiner contends that the phrase "a composition obtained by the process according to claim 22" is indefinite and ambiguous. More specifically, the Examiner contends that it is unclear what the composition is.

Applicant respectfully traverses the Examiner's rejection and the arguments and contentions set forth in support thereof for the following reasons. Claim 33 clearly sets forth the subject matter thereof as including a composition obtained by a process comprising reacting a compound of the formula (I) and a compound of the formula (II). The compounds (I and II) are defined in the claims via definitions of substituents and variables in a clear and ordinary manner.

As described in the Specification, a reaction of a compound of formula (I) and a compound of formula (II) can result in a mixture of various compounds (*i.e.*, a composition), including various products (such as a compound of formula (III) and a compound of formula (IV)) and excess reactants, which may be present depending upon the molar ratio of reactants

used. The products and reactants may be in solution and some may have precipitated, depending upon the reaction system and solvent used in relation to the particular solubility of the products.

The main product obtained by reacting a compound of formula (I) and a compound of formula (II), as described in Applicant's Specification, is a compound of formula (III) in which the (B'H) moieties of the compound of the formula (II) are ionically bound to the ruthenium complex of the compound of the formula (I). An additional product of the reaction of the compound of the formula (I) and a compound of the formula (II) is the salt of the metal (M) of the compound of the formula (I) and the X' substituent of the compound of the formula (II). Additionally, as stated above, the reaction mixture may additionally include excess reactants, depending upon the molar ratio used in the reaction. Also, the products and/or reactants may be present as solvated ions or precipitated solids. The solubility of the indazolium salts of the ruthenium complexes appear to be significantly lower than the solubility of the corresponding sodium salt reactants, and thus, the indazolium complex (*i.e.*, compounds of formula (III)) would likely be the first to precipitate as the solubility limit thereof is reached.

Thus, the compositions of claim 33 include the products of a reaction between a compound of formula (I) and a compound of formula (II) (*i.e.*, a mixture of a compound of formula (III) and a compound of formula (IV)), along with any excess reactants used in the reaction.

Furthermore, the claim is sufficiently clear and definite as compositions obtained by reacting a compound of the formula (I) and a compound of the formula (II) are fully described throughout the Specification in various embodiments and specifically, for example, with respect to the description of one of the "kits" disclosed in the Specification at Paragraph [0073], wherein a compound of formula (I) and a compound of formula (II) can be reacted to form a composition (A), comprising an indazolium salt of a ruthenium complex (*i.e.*, a compound of formula (III)) and sodium chloride (*i.e.*, a compound of formula (IV)), as shown in Fig. 1 at page 11 of the Specification.

Accordingly, Applicant respectfully submits that the rejected claim is not indefinite and complies with the requirements of §112, second paragraph. Thus, reconsideration and withdrawal of the rejection are respectfully requested.

In the Office Action, the Examiner rejects claims 33-37 under 35 U.S.C. §102(b) as being anticipated by U.S. Patent No. 4,843,069 of Keller, *et al.* ("Keller"). Specifically, the Examiner contends that Keller discloses a composition comprising various compounds (*e.g.*, ruthenate complexes). The Examiner contends that Keller clearly anticipates the instantly claimed compositions on that basis.

Applicant strenuously, but respectfully, traverses the Examiner's rejection and the arguments and contentions set forth in support thereof for the following reasons. To begin with, Applicant's claimed invention is directed to a composition obtained by reacting a compound of formula (I) and a compound of formula (II). As described above, the claimed product composition comprises a compound of formula (III) and a compound of formula (IV). As described throughout the Specification, the inventive process provides a reaction product mixture which enhances the solubility of various indazolium salts of ruthenate complexes which can enhance the suitability of the compositions for the intended use of treating various tumors. Thus, the claimed compositions are mixtures of reaction products (*i.e.*, compounds of formula (III) and compounds of formula (IV)), along with, for example, excess reactant.

In contrast, Keller is directed to the synthetic preparation of individual compounds which correspond to the formula (I) set forth in Keller at col. 1, lines 30-47. More specifically, at col. 4, lines 14-22, the specific synthetic route for the disclosed ruthenium complex compounds is set forth, wherein the nitrogen-heterocyclic compounds are added to a solution of ruthenium (III) chloride or bromide. The product separates or is precipitated by the addition of an organic solvent or through concentrating the reaction solution and/or cooling. However, Keller does not disclose compositions which comprise a mixture of reaction products, including a compound of Applicant's formula (III) and a compound of Applicant's formula (IV), as claimed in the instant application. Accordingly, Keller does not anticipate the claimed

invention. Reconsideration and withdrawal of the rejection under 35 U.S.C. §102(b), based upon Keller, are respectfully requested.

In the Office Action, the Examiner rejects claims 33-39 under 35 U.S.C. §103(a), as being unpatentable over Keller, in view of Peti, *et al.* European Journal of Inorganic Chemistry, Vol. 9, pp. 1551-55 (1999) (hereinafter referred to as "the EJIC publication" and incorrectly referred to as "the Keller publication" by the Examiner). Specifically, the Examiner contends that Keller discloses a ruthenium complex as described above, with respect to the rejection under §102(b). The Examiner contends that the difference between the instant claims and Keller is the variable X and X' of the instantly claimed compositions. The Examiner argues that the EJIC publication discloses sodium salts of ruthenate complexes and that the sodium salts of the complexes are more soluble in water. Thus, the Examiner argues that one of ordinary skill in the art "would be motivated to employ the compounds of Keller, *et al.* '069 and the inherent teachings of Keller, *et al.* [the EJIC publication] to obtain instant claimed compositions, *i.e.*, a composition obtained from reacting compounds of formula (I) and (II) or a composition obtained by mixing compounds of formula (III) and (IV), ..." (*See*, the Office Action, page 12).

Applicant respectfully traverses the Examiner's rejections and the arguments and contentions set forth in support thereof for the following reasons. To begin with, Applicant submits, as set forth above, that Keller fails to disclose the presently claimed compositions, which comprise the reaction products of the reaction of a compound of claimed formula (I) and formula (II). Keller only teaches the specific ruthenate complexes disclosed therein obtained by a synthetic route from which the ruthenate complexes are isolated. There is no teaching or suggestion in Keller which would motivate one of ordinary skill in the art to react a compound of formula (I) and a compound of formula (II), as claimed.

Additionally, the EJIC publication fails to remedy the deficiencies of Keller. The EJIC publication is directed to various synthetic routes of providing a sodium salt of a ruthenate complex. (*See*, the EJIC publication, page 1552, Fig. 1). In other words, the EJIC publication is directed to routes for the synthesis of a compound of formula (I) as set forth in the instant application. Thus, the EJIC publication teaches forming one of Applicant's reactants. There is

nothing in the Keller publication which would motivate one of ordinary skill in the art to then take the formed sodium ruthenate complexes of the EJIC publication and subsequently react the sodium complex with a compound of formula (II) (as claimed), in order to arrive at Applicant's inventive compositions. Moreover, Applicant respectfully submits that there is nothing inherently disclosed in the EJIC publication which would motivate one of ordinary skill in the art to further react the disclosed end product of the EJIC publication with a further reactant to provide a composition comprising a mixture as claimed.

Thus, Applicant submits that neither Keller nor the EJIC publication teaches or suggests each and every element of Applicant's claimed as neither reference teaches the reaction of the compounds recited in Applicant's claims. Moreover, Applicant respectfully submits that there is no teaching or suggestion in either of the cited references which would motivate one of ordinary skill in the art to combine and modify the references as suggested by the Examiner to arrive at Applicant's claimed invention. Finally, it cannot reasonably be said that one of ordinary skill in the art would expect to successfully prepare a tumor inhibiting ruthenate complex by diverging from the explicit teachings of the references, such as by further reacting the end product disclosed in the EJIC publication. Accordingly, Applicant submits that the Examiner has failed to establish a *prima facie* case of obviousness based upon the cited references. Thus, reconsideration and withdrawal of the rejection under §103(a) are respectfully requested.

Finally, in the Office Action, the Examiner rejects claims 33-39 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 4 of Keller, in view of the EJIC publication. Applicant respectfully traverses this rejection and the contentions and arguments set forth in the Office Action in support thereof. More specifically, Applicant refers to the comments set forth above with respect to the rejection under 35 U.S.C. §103(a) based upon these two references. As discussed above, Applicant respectfully submits that the claimed invention in the instant application is not obviated by the combination of Keller and the EJIC publication as neither reference teaches or suggests the claimed reaction or resulting composition.

Accordingly, Applicant respectfully requests reconsideration and withdrawal of the Examiner's rejection under the judicially created doctrine of obviousness-type double patenting.

In view of the Remarks set forth herein and the accompanying Declaration under 37 C.F.R. §1.132, Applicant respectfully submits that the pending claims are enabled, comply with the written description requirement, are definite and patentably distinguish over the prior art of record and known to Applicant. Accordingly, reconsideration, withdrawal of all rejections and a Notice of Allowance are respectfully requested.

Respectfully submitted,
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Enclosures – Petition for Extension of Time (two months)
Declaration of Nikolai Graf v. Keyserlingk, Ph.D. under 37 C.F.R. §1.132